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(71) Applicant: **RICERCHE DI SCHIENA S.N.C. DEL  
DR. MICHELE G. DI SCHIENA & C.**  
**Via Garibaldi, 17**  
**I-20080 Cisliano (Milano)(IT)**

Applicant: **RICERFARMA Srl**  
**Via Moisé Loria 75**  
**Milano(IT)**

(72) Inventor: **Di Schiena, Michele Giuseppe**  
**Via Garibaldi, 17**  
**I-20080 Cisliano (Milan)(IT)**

(74) Representative: **Gervasi, Gemma et al**  
**NOTARBARTOLO & GERVASI Srl Viale**  
**Bianca Maria 33**  
**I-20122 Milan(IT)**

(54) **Topically administered compositions based on high molecular weight hyaluronic acid for treating inflammations of the oral cavity, and for oral cavity hygiene and cosmetic treatment.**

(57) The use of the sodium salt of hyaluronic acid of molecular weight between 800,000 and 4,000,000 as active principle in the preparation of pharmaceutical compositions for topical application both for the therapy and prophylaxis of inflammatory affections of the oral cavity, and for oral cavity cosmetic treatment and hygiene.

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**TOPICALLY ADMINISTERED COMPOSITIONS BASED ON HIGH MOLECULAR WEIGHT HYALURONIC ACID FOR TREATING INFLAMMATIONS OF THE ORAL CAVITY, AND FOR ORAL CAVITY HYGIENE AND COSMETIC TREATMENT**

This invention relates to the use of the sodium salt of high molecular weight hyaluronic acid as active principle in the preparation of pharmaceutical compositions for topical application for the therapy and prophylaxis of inflammatory affections of the oral cavity, and for hygienic and cosmetic treatment of the oral cavity.

5 Hyaluronic acid is the most important asulphurated mucopolysaccharide acid of the fundamental matter of the connective tissue, both from the strictly biochemical and from the physiological viewpoints.

In man, hyaluronic acid is present not only in the connective tissue but also in the important biological fluids such as vitreous humor, aqueous humor, etc. and in the umbilical cord.

It has practically zero toxicity, and specific contraindications for human use are not known.

10 As in the case of other components of natural substances, hyaluronic acid can be obtained by extraction from the relative natural substances, for example it can be extracted from chicken crests, or can be produced biotechnologically.

Hyaluronic acid has a very wide range of molecular weights, which can vary from 30,000 to more than 15,000,000, depending on the type of process used.

15 Said acid has been used in the form of its sodium salt for some time, both in human therapy and in cosmetic treatment.

In this respect the exogenous application of hyaluronic acid has a beneficial effect in favouring the connective organization, and in addition it opposes the inflammatory process induced by hyaluronidase-producing germs; it facilitates resolution of the phlogistic component, reduces abnormal capillary permeability, accelerates tissue repair processes and it performs an antiedematogenic action by metabolically binding free water to its molecular structures.

The therapeutic indications for hyaluronic acid are numerous, including abrasive-excoriative dermatopathies, ulcers deriving from arteriosclerotic vasculopathies, varicose ulcers, cicatrization delays and surgical excisions.

25 In cosmetic practice hyaluronic acid is used for its restorative, tonicizing, dermo-reparation, cicatrizing and hydrating properties. For example in USP 4,736,024 hyaluronic acid or a salt thereof is used as a vehicle for pharmacologically active substances in pharmaceutical compositions which can be topically administered.

30 This patent describes the use of hyaluronic acid in pharmaceutical compositions for application to the oral cavity, however in this patent the hyaluronic acid is used only as a vehicle which allows faster absorption of the topically applied active principle. Moreover, the compositions amply described and claimed in it are for ophthalmic and dermatological treatment.

35 It is therefore probable that prolonged therapeutic use in the oral cavity of hyaluronic acid associated with medicaments presents risks due to the possible side effects of the medicament on the gingival tissue and risks connected with the inevitable ingestion of the medicament itself.

The compositions described in this patent can hardly be used for practical preventive hygiene.

Hyaluronic acid has been used as active principle with success in the therapy of different parodontopathies by injecting it submucously directly into the gingiva (F. Brandimarte, Min. Stom. 17, 140-156, 1968).

40 This type of hyaluronic acid administration is strictly under the competence of the specialized doctor and in addition there are infiltration-related risks, and moreover it cannot be used extensively since it is unpleasant for the patient.

Furthermore, such an administration cannot be used for the more common inflammatory pathologies of the gingiva, which are the most common.

45 It has now been surprisingly found that hyaluronic acid in sodium salt form and characterised by a molecular weight of between 800,000 and 4,000,000, preferably between 1,000,000 and 2,000,000, can be used as active principle in the preparation of pharmaceutical compositions for topical administration in the treatment and prophylaxis of inflammatory affections of the oral cavity and for cosmetic treatment and hygiene of the oral cavity. Consequently the present invention provides topically administered pharmaceutical compositions for the prophylaxis and treatment of the oral cavity and for oral cavity cosmetic treatment and relative hygiene, containing as active principle hyaluronic acid characterised by an average molecular weight of between 800,000 and 4,000,000, and preferably between 1,000,000 and 2,000,000.

The compositions according to the invention generally contain from 0.005% to 10% of Sodium

Hyaluronate.

The compositions according to the present invention for therapeutic use generally contain between 0.2 and 10% by weight, based on the total composition weight, and preferably between 0.2 and 1% by weight of said active principle.

5 The compositions according to the present invention for oral cavity prophylactic, cosmetic and hygienic use contain between 0.005 and 0.1% by weight, based on the total composition weight, of said active principle. The latest preferably contain 0.01% by weight of sodium hyaluronate.

The compositions according to the present invention are administered topically and can be in the form of gingival pastes, toothpastes, mouthwashes and adhesive pastes and powders.

10 The pharmaceutical compositions according to the present invention generally contain conventional excipients, for example polyalcohols such as sorbitol and/or maltitol, glycols such as polyethyleneglycol, thickeners such as carboxymethylcellulose, preservatives such as methyl or propyl paraoxybenzoate, flavouring agents such as peppermint, sweeteners such as saccharin, and colouring agents.

The compositions according to the present invention for therapeutic use are advantageously used for 15 gingival affections, characterised by inflammatory manifestations of the gingival tissue, such as gingivitis, stomatitis, irritations due to mechanical causes such as fixed or mobile prostheses or surgical operations etc.

The gingival pastes according to the present invention can also be used during the dentition stage in children.

20 The following examples are given for the purpose of illustrating the present invention but without implying any limitation thereon.

#### EXAMPLE 1 Gingival paste in gel form

25 5 g of sodium hyaluronate of molecular weight 1,000,000 are carefully dispersed in 70 ml of water containing a preservative. 25 g of 70% sorbitol are added and the mixture is carefully mixed.

#### EXAMPLE 2 Gingival paste in gel form

30 54 g of sodium carboxymethylcellulose of medium viscosity type are dispersed in 774 g of water (containing 0.13% of p-oxybenzoate and 0.007% of propyl p-oxybenzoate as preservatives).

240 g of an aqueous solution containing 1% of sodium hyaluronate (molecular weight 1,500,000) are added followed by 120 g of 70% sorbitol.

The system is stirred until a homogeneous transparent mass is obtained, which is then flavoured with 6 35 g of peppermint.

#### EXAMPLE 3 Gingival paste in gel form

Example 2 is repeated but using a 70% aqueous maltitol solution instead of the 70% sorbitol.

#### 40 EXAMPLE 4 Toothpaste

A toothpaste is prepared by mixing the following components in the indicated proportions, which are by weight:

45	amorphous silica	18.00%
	sorbitol	74.5%
50	sodium carboxymethylcellulose	0.2%
	sodium hyaluronate (average M.W. 1,500,000)	0.1%
55	saccharin	0.20%

	50% aqueous NaOH	0.30%
	lauryl sulphate	1.50%
5	sodium monofluorosulphate	0.85%
	water	3 %
10	flavouring agents	1 %
	colouring agents as required	

## 15 EXAMPLE 5 Mouthwash

The mouthwash is prepared by mixing the following components in the indicated proportions.

20	Deionized water FU	98 g
	sodium hyaluronate (average M.W. 1,500,000)	0.01%
	preservative as required	
25	flavouring agents as required	

## 30 EXAMPLE 6 Adhesive powder for dentures

An adhesive powder for dentures is prepared by mixing the components in the following proportions:

35	high viscosity sodium carboxymethylcellulose	70%
	sodium hyaluronate (average M.W. 2,000,000)	1%
	polyethoxylated polymer	28%
40	peppermint flavour	1%

## 45 EXAMPLE 7 Adhesive paste for dentures

An adhesive paste for dentures is prepared by mixing the following components in the indicated proportions:

50	sodium hyaluronate (average M.W. 1,500,000)	0.2%
	lidocaine	4 %
55	phenol	0.1%
	white vaselin	57.7%

The gingival paste prepared in Example 2 containing 0.2% of sodium hyaluronate of average molecular weight 1,500,000 was tested on 10 patients.

The chosen patients showed various degrees of parodontal pathology. The first group comprising 6 patients suffered from simple marginal gingivitis, whereas the second group comprising the remaining 4 patients had undergone parodontal surgery.

With the first group it was noted that the topical use of the gingival paste containing hyaluronic acid resulted always by the second day in a reduction in symptomatology, characterised essentially by hypersensitivity to heat stimuli and slight bleeding on brushing, with complete recovery within one week.

With the second group examined, recovery was slower due essentially to the fact that a surgical wound was present which alone required about one week for recovery.

For this reason the compound was applied only during the latter stages of recovery mainly because the wound was protected by a parodontal compress. A clear improvement in condition was also noted in this group, to the extent that on termination of treatment the mucosa at the wound level was trophic and pink-coloured.

In conclusion the product was of considerable help in recovery, in that with the first group it participated in normal oral hygiene and with the second group it facilitated the normal physiological reparation processes.

Tests were conducted on the same patients with other compositions deriving from the aforesaid examples, the results obtained being comparable with those described.

## Claims

1. The use of hyaluronic acid in the form of its sodium salt, characterised by an average molecular weight of between 800,000 and 4,000,000, as active principle in the preparation of pharmaceutical compositions for topical application both for the therapy and prophylaxis of inflammatory affections of the oral cavity, and for hygiene and cosmetic treatment of the oral cavity.
2. The use of hyaluronic acid in the form of its sodium salt as claimed in claim 1, characterised in that the average molecular weight of the hyaluronic acid is between 1,000,000 and 2,000,000.
3. Pharmaceutical compositions containing the sodium salt of hyaluronic acid as active principle in accordance with one of the preceding claims in combination with excipients, for the therapeutic and prophylactic treatment of inflammatory affections of the oral cavity, and for oral cavity hygiene and cosmetic treatment.
4. Pharmaceutical compositions as claimed in claim 3, containing the active principle in amounts ranging from 0.005 to 10% by weight based on the total composition weight.
5. Pharmaceutical compositions for the therapeutic treatment of inflammatory affections of the oral cavity as claimed in claim 4, containing the active principle in amounts ranging from 0.2 to 10% by weight based on the total composition weight.
6. Pharmaceutical compositions for the therapeutic treatment of inflammatory affections of the oral cavity as claimed in claim 5, containing the active principle in amounts ranging from 0.2 to 1% by weight based on the total composition weight.
7. Pharmaceutical compositions for the prophylaxis, cosmetic treatment and hygiene of the oral cavity as claimed in claim 4, containing the active principle in a concentration of between 0.005 and 0.1% by weight based on the total composition weight.
8. Pharmaceutical compositions as claimed in claim 7, containing the active principle in a concentration of 0.01% by weight, based on the total composition weight.
9. Pharmaceutical compositions as claimed in claim 3, in the form of gingival pastes, toothpastes, mouthwashes and adhesive pastes and powders.
10. Pharmaceutical compositions as claimed in one of claims 5 and 6 for the treatment of gingivitis, stomatitis and irritation due to mechanical causes or surgery.

11. Gingival pastes as claimed in claim 9 for the dentition stage in children.

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## EUROPEAN SEARCH REPORT

Application Number

EP 91 10 2240

### DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	PHARMACOMETRICS, vol. 28, no. 6, 1984, pages 1123-1135; K. MIYAZAKI et al.: "Studies on analgesic and anti-inflammatory effects of sodium hyaluronate (SPH)" * Summary * - - -	1-3	A 61 K 31/725
X	PATENT ABSTRACTS OF JAPAN, vol. 7, no. 118 (C-167)[1263], 21st May 1983; & JP-A-58 37 001 (MIDORI JUJI K.K.) 04-03-1983 * Abstract * - - -	1-3	
X	CHEMICAL ABSTRACTS, vol. 99, no. 26, 26th December 1983, page 382, abstract no. 218566e, Columbus, Ohio, US; & JP-A-58 84 801 (GREEN CROSS CORP.) 21-05-1983 * Abstract * - - -	1-3	
X	CHEMICAL ABSTRACTS, vol. 99, no. 16, 17th October 1983, page 356, abstract no. 128315t, Columbus, Ohio, US; & JP-A-58 37 001 (GREEN CROSS CORP.) 04-03-1983 * Abstract * - - -	1-3	
D,X	MIN. STOM., vol. 17, 1968, pages 140-156; F. BRAN-DIMARTE: "Acido ialuronico e parodontopatie" * Summary * - - -	1-11	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	WO-A-8 404 453 (ANDERSSON) * Abstract; claims * - - -	1-11	A 61 K
A	EP-A-0 138 572 (FIDIA S.p.A.) * Page 3, line 1 - page 6, line 12; claims *	1-11	
X	EP-A-0 243 867 (MOBAY CORP.) * Abstract; page 3, lines 21-32; page 4, line 41 - page 5, line 4; page 5, lines 19-52; claims * - - - -/-	1-11	
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		14 May 91	GOETZ G.
<div><div><b>CATEGORY OF CITED DOCUMENTS</b> X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</div><div>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons ----- &amp;: member of the same patent family, corresponding document</div></div>			



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Application Number

**EP 91 10 2240**

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 197 718 (FIDIA S.p.A.) * Abstract; page 4, line 18 - page 5, line 26; page 10, line 4 - page 14, line 29; claims * - - -	1-11	
A	WO-A-8 807 060 (ARTHROPHARM PTY. LTD) * Abstract; page 4, line 33 - page 5, line 21; page 15, line 25 - page 17, line 14; claims * - - - - -	1-11	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		14 May 91	GOETZ G.
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone  Y : particularly relevant if combined with another document of the same category  A : technological background  O : non-written disclosure  P : intermediate document  T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date  D : document cited in the application  L : document cited for other reasons  &amp; : member of the same patent family, corresponding document</p>			